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Development of the UV-spectrophotometric and extraction-spectrophotometric methods of the atomoxetine quantitative determination suitable for the chemical and toxicological analysis

The acute and lethal antidepressant poisonings have the tendency to grow, therefore, development of the methods for its chemical and toxicological analysis is a topical issue.

Aim. To develop and validate the methods for the quantitative determination of atomoxetine, an antidepressant, using available and widely spread methods in the chemical and toxicological analysis practice, such as UV spectrophotometry and extraction-spectrophotometry in the visible region of the spectrum with methyl orange, an acidic azo dye.

Materials and methods. Absorbance values of the solutions in the UV and visible regions of the spectrum were measured on a SF-46 spectrophotometer (LOMO), the spectral measurement range was from 190 to 1100 nm. The standard solution of atomoxetine in 0.1 M hydrocloric acid (300 μg/ml) was used for the UV spectrophotometric study, and the standard solution of atomoxetine in water (150 μg/ml) was used for the extraction spectrophotometry in the visible region.

Results and discussion. The calibration curve for the UV spectrophotometric method was described by the equation of $y = (0.00455 \pm 4 \cdot 10^{-5})x + (0.016 \pm 0.005)$; linearity was observed within the atomoxetine concentration range of 15.0-210 μg/ml; *LOD* and *LOQ* were 1.8 μg/ml and 5.6 μg/ml, respectively. The calibration curve for the extraction spectrophotometric method was described by the equation of $y = (0.00808 \pm 5 \cdot 10^{-5})x$; linearity was observed within the atomoxetine concentrations of 15.0-150.0 μg in a sample; *LOD* and *LOQ* were 1.4 μg and 4.3 μg in a sample, respectively.

Conclusions. The methods developed for the quantitative determination of atomoxetine using the UV-spectrophotometric method and extraction spectrophotometry in the visible region of the spectrum satisfy the requirements set to the methods recommended for use in the forensic toxicology, and it has been confirmed by the validation characteristics.

Key words: *atomoxetine; UV-spectrophotometry; extraction spectrophotometry in the visible region of the spectrum*

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Розробка УФ-спектрофотометричного та екстракційно-спектрофотометричного методів кількісного визначення атомоксетину, придатних для хіміко-токсикологічного аналізу

Кількість гострих та летальних отруєнь лікарськими препаратами антидепресивної дії має тенденцію до зростання, що робить актуальним розробку методів їх хіміко-токсикологічного аналізу.

Метою даних досліджень є розробка і валідація методик кількісного визначення антидепресанта атомоксетину за допомогою доступних та широко впроваджених у практику хіміко-токсикологічного аналізу методів УФ-спектрофотометрії та екстракційної спектрофотометрії у видимій області спектра з кислотним азобарвником метиловим оранжевим.

Матеріали та методи. Світлопоглинання розчинів в УФ- та видимій областях спектра вимірювали на спектрофотометрі СФ-46 (ЛОМО), спектральний діапазон вимірювань – від 190 до 1100 нм. Використовували стандартний розчин атомоксетину в 0,1 М кислоті хлоридній (300 мкг/мл) для УФ-спектрофотометричних досліджень і стандартний розчин атомоксетину у воді (150 мкг/мл) для досліджень методом екстракційної спектрофотометрії у видимій області.

Результати та їх обговорення. Калібрувальний графік для УФ-спектрофотометричного методу описувався рівнянням: $y = (0{,}00455 \pm 4 \cdot 10^{-5})x + (0{,}016 \pm 0{,}005)$; лінійність спостерігали в межах концентрацій атомоксетину 15,0-210 мкг/мл; *LOD* та *LOQ* становили, відповідно, 1,8 мкг/мл та 5,6 мкг/мл. Калібрувальний графік для екстракційно-спектрофотометричного методу описувався рівнянням: $y = (0{,}00808 \pm 5 \cdot 10^{-5})x$; лінійність спостерігали в межах концентрацій атомоксетину 15,0-150,0 мкг в пробі; *LOD* та *LOQ* становили, відповідно, 1,4 мкг та 4,3 мкг в пробі.

Висновки. Розроблені методики кількісного визначення атомоксетину з використанням УФ-спектрофотометричного методу та екстракційної спектрофотометрії у видимій області спектра задовольняють вимогам щодо методів, рекомендованих для використання в судовій токсикології, що підтверджено валідаційними характеристиками.

Ключові слова: *атомоксетин; УФ-спектрофотометрія; екстракційна спектрофотометрія у видимій області спектра*

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Разработка УФ-спектрофотометрического и экстракционно-спектрофотометрического методов количественного определения атомоксетина, пригодных для химико-токсикологического анализа

Количество острых и летальных отравлений лекарственными препаратами антидепрессивного действия имеет тенденцию к росту, что делает актуальным разработку методов их химико-токсикологического анализа.

Целью данных исследований является разработка и валидация методик количественного определения антидепрессанта атомоксетина с помощью доступных и широко внедренных в практику химико-токсикологического анализа методов УФ-спектрофотометрии и экстракционной спектрофотометрии в видимой области спектра с кислотным азокрасителем метиловым оранжевым.

Материалы и методы. Светопоглощение растворов в УФ- и видимой областях спектра измеряли на спектрофотометре СФ-46 (ЛОМО), спектральный диапазон измерений – от 190 до 1100 нм. Использовали стандартный раствор атомоксетина в 0,1 М кислоте хлоридной (300 мкг/мл) для УФ-спектрофотометрических исследований и стандартный раствор атомоксетина в воде (150 мкг/мл) для исследований методом экстракционной спектрофотометрии в видимой области.

Результаты и их обсуждение. Калибровочный график для УФ-спектрофотометрического метода описывался уравнением: $y = (0{,}00455 \pm 4 \cdot 10^{-5})x + (0{,}016 \pm 0{,}005)$; линейность наблюдали в пределах концентраций атомоксетина 15,0-210 мкг/мл; *LOD* и *LOQ* составили, соответственно, 1,8 мкг/мл и 5,6 мкг/мл. Калибровочный график для экстракционно-спектрофотометрического метода описывался уравнением: $y = (0{,}00808 \pm 5 \cdot 10^{-5})x$; линейность наблюдали в пределах концентраций атомоксетина 15,0-150,0 мкг в пробе; *LOD* и *LOQ* составили, соответственно, 1,4 мкг и 4,3 мкг в пробе.

Выводы. Разработанные методики количественного определения атомоксетина с использованием УФ-спектрофотометрического метода и экстракционной спектрофотометрии в видимой области спектра удовлетворяют требованиям к методам, рекомендованным для использования в судебной токсикологии, что подтверждено валидационными характеристиками.

Ключевые слова: *атомоксетин; УФ-спектрофотометрия; экстракционная спектрофотометрия в видимой области спектра*

Atomoxetine ((3R)-*N*-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine hydrochloride) is an antidepressant drug used in the treatment of attention deficit hyperactivity syndrome, as well as the therapeutically resistant depression [1]. Repeated episodes of acute and lethal atomoxetine poisoning were registered [2, 3, 4]. The postmortem atomoxetine concentrations were within the following limits: arterial blood – 0.1-8.3 mg/l; bile – 1.0-33 mg/l; urine – 0.1 mg/l; liver – 0.44-29 mg/kg [4].

The methods of atomoxetine determination in the blood plasma using high-performance liquid chromatography with UV- [5, 6], fluorescence [7], mass spectrometry detection [8], or capillary electrophoresis [9] have been developed. These methods of analysis are highly sensitive and specific, but require careful sample preparation and special expensive equipment; as a result, they are not always available.

Methods of molecular absorption spectroscopy in the UV and visible region of the spectrum allow determining the toxic and lethal concentrations of toxicants in the biological samples and can be recommended for use in the forensic toxicology [10, 11, 12].

The aim of the study was to develop and validate the methods for the quantitative determination of atomoxetine, an antidepressant, using available and widely spread methods in the chemical and toxicological analysis practice, such as UV spectrophotometry and extraction-spectrophotometry in the visible region of the spectrum with methyl orange, an acidic azo dye.

Materials and methods

The pure substance of atomoxetine isolated by the method described in the article [13] from the medicine "Strattera" (7 capsules, 60 mg) produced by "Lilly" (Czech Republic) was used for the study.

Absorbance values of the solutions in the UV and visible regions of the spectrum were measured on a SF-46 spectrophotometer (LOMO), the spectral measurement range was from 190 to 1100 nm.

Buffer solution pH was monitored by a pH-meter 5123 (Elvro, Wroclaw, Poland).

The following glassware was used: 10.0 ml, 50.0 ml volumetric flasks, volumetric pipettes, Class A (Simax, Czech Republic).

All other chemicals were of analytical grade or better.

The method of the calibration curve construction for the UV spectrophotometric determination. Prepare the stock solution (SS) and six working standard solutions (WSS) of atomoxetine hydrochloride ($m = 6$) in 0.1 M hydrochloric acid. For this purpose dissolve 0.01715 g of atomoxetine hydrochloride (corresponding to 0.01500 g of the atomoxetine base) in 50.0 ml of 0.1 M hydrochloric acid using a 50.0 ml volumetric flask (the concentration of the resulting SS is 300 μg/ml of the atomoxetine base). Then place 0.50; 1.00; 2.00; 3.0; 4.0; 5.0; 6.0 and 7.0 ml of SS into a 10.0 ml volumetric flask and dilute to the volume with 0.1 M hydrochloric acid (the concentrations of the resulting WSS are of 15.0; 30.0; 60.0; 90; 120; 150; 180 and 210 μg/ml of the atomoxe-

Table 1

The accuracy and precision of the UV spectrophotometric method (*intra day*)

Introduced, μg/ml	Absorbance	Found, μg/ml	Found/introduced, %	Average, %	SD	*RSD*, %	ε, %
15	0.084	14.95	99.63	99.07	0.970	0.98	2.43
	0.084	14.95	99.63				
	0.083	14.69	97.95				
90	0.430	91.00	101.10	100.77	0.783	0.78	1.93
	0.425	89.89	99.88				
	0.431	91.21	101.34				
180	0.827	178.24	99.02	99.19	0.511	0.52	1.28
	0.833	179.56	99.76				
	0.825	177.80	98.78				

tine base, respectively). Measure the absorbance values of WSS at a wavelength of 270 nm in a 10 mm light pathway cuvette. Use 0.1 M hydrochloric acid as a reference solution. Examine each WSS twice (n = 2).

The method of the calibration curve construction for the quantitative determination by the extraction spectrophotometry in the visible region of the spectrum. Prepare the stock solution (SS) of atomoxetine hydrochloride in water. For this purpose dissolve 0.01715 g of atomoxetine hydrochloride (corresponding to 0.01500 g of the atomoxetine base) in 100.0 ml of distilled water using a 100.0 ml volumetric flask (the concentration of the resulting SS is 150 μg/ml of the atomoxetine base). Study six calibrators with a different drug content ($m = 6$), examining each three times ($n = 3$). For this purpose place 5.0 ml of acetate buffer with pH 4.6, 5.0 ml of 0.05 % methyl orange solution and 0.1; 0.2; 0.3; 0.4; 0.6 and 1.0 ml of SS (the resulting solutions contain 15.0; 30.0; 45.0; 60.0; 90.0 and 15.0 μg of the atomoxetine base in a sample, respectively). Add in all cases, except the last one, the appropriate volumes of distilled water (from 0.90 to 0.40 ml) with the constant volume of the aqueous phase. Add 15.0 ml of chloroform to the mixtures obtained. Shake the mixtures using the separating funnels for 10 min with the help of a mechanical shaker and left for 10 min for separating the layers. Collect 14 ml of the resulting chloroform layers discarding the first portions (about 1 ml), then add to the chloroform layers 2 ml of 1 % sulphuric acid solution in absolute ethanol. Mix the solutions obtained thoroughly and measure the absorbance values at λ_{max} = 540 nm in a 10 mm light pathway cuvette. Use the blank solution as a reference.

Results and discussion

The absorbance values in the UV region of the spectrum for eight SSR of atomoxetine ($m = 8$; $n = 2$) were processed by the linear regression model described in the general form as $y = bx + a$. The significance of the regression coefficient a in the regression model was checked using the F-test [14], and the conclusion was drawn that it was impossible to have the equation in the form of $y = b'x$. Thus, the calibration curve was described by the equation of $y = (0.00455 \pm 4 \cdot 10^{-5})x + (0.016 \pm 0.005)$ ($r = 0.999$; $S_o^2 = 3 \cdot 10^{-5}$; $S_a = 2.49 \cdot 10^{-3}$; $S_b = 4 \cdot 10^{-5}$). Atomoxetine showed linearity in the range of 15.0-210 μg/ml. The *LOD* and *LOQ* values were calculated using standard deviation of intercept (S_a) in accordance with the relevant equations: $LOD = 3.3 \cdot S_a^2/b$ and $LOQ = 10 \cdot S_a^2/b$ [15, 16]. They were 1.8 μg/ml and 5.5 μg/ml, respectively.

The accuracy and precision of the method were determined at three concentration levels within one day (*intra day*) (Tab. 1) and over three consecutive days (*inter day*). The number of replicates per a concentration level and day was three.

The "inter day" accuracy and precision were 99.23 % (*RSD* = 0.83 %) at the low concentration level of the analyte, 100.88 % (*RSD* = 0.41 %) at the middle concentration level, 99.28 % (*RSD* = 0.21 %) at the high concentration level.

Table 2

The accuracy and precision of the extraction spectrophotometric method (*intra day*)

Introduced, μg	Absorbance	Found, μg	Found/introduced, %	Average, %	SD	*RSD*, %	ε, %
15	0.120	14.85	99.01	101.21	2.074	2.05	5.09
	0.125	15.47	103.13				
	0.123	15.22	101.49				
60	0.485	60.02	100.04	100.43	1.450	1.44	3.59
	0.480	59.41	99.00				
	0.494	61.14	101.90				
150	1.223	15.36	100.91	99.59	1.460	1.47	3.63
	1.188	14.03	98.02				
	1.210	149.75	99.83				

The absorbance values in the visible region of the spectrum for six calibration standards of atomoxetine ($m = 6$; $n = 3$) were processed by the linear regression model. The significance of the regression coefficient a in the regression model was checked using the F-test [14], and the conclusion was drawn that it was possible to have the equation in the form of $y = b'x$. Thus, the calibration curve was described by the equation of $y = (0.00808 \pm 5 \cdot 10^{-5})x$ ($r = 0.999$; $S_o^2 = 7 \cdot 10^{-5}$; $S_a = 3.5 \cdot 10^{-3}$; $S_b = 5 \cdot 10^{-5}$). Atomoxetine showed linearity in the range of 15.0-150.0 μg in a sample. The *LOD* and *LOQ* values were calculated using standard deviation of intercept and the slope of the calibration curve [15, 16]. They were 1.4 μg and 4.3 μg in a sample, respectively (Tab. 2).

The "inter day" accuracy and precision were 101.39 % (*RSD* = 2.18 %) at the low concentration level of the analyte, 100.08 % (*RSD* = 0.81 %) at the middle concentration level, 99.84 % (*RSD* = 1.05 %) at the high concentration level.

CONCLUSIONS

The methods developed for the quantitative determination of atomoxetine using the UV-spectrophotometric method and extraction spectrophotometry in the visible region of the spectrum satisfy the requirements set to the methods recommended for use in the forensic toxicology [12, 16], and it has been confirmed by the validation characteristics.

Conflict of Interests: authors have no conflict of interests to declare.

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